INTRODUCTION

Membranous nephropathy is a pathological diagnosis found in 6% of all patients who have a renal biopsy to evaluate proteinuria and up to 33% of adults who present with the nephrotic syndrome. It remains a common cause of end-stage renal disease throughout the world. The aetiological agent is unknown in 70–80% of cases and the disorder is termed idiopathic, whereas in the other 20–30% a defined agent can be determined and the disease is categorized as secondary (see Table 1). The depth of the search for secondary causes varies by both the age of the patient and his geography. In Africa, for instance, an infectious cause such as malaria is common, and in Asia, hepatitis B is a frequent aetiological agent. The issue of age relates to the association of malignancy with membranous nephropathy. This association is stronger in the age group above 55 years. In patients < 55 years, a search for an occult malignancy in the absence of any signs or symptoms should be limited, but investigations should probably include a chest radiograph, a stool examination for occult blood, mammography in women and, perhaps, a prostate-specific antigen test in men. The surveillance should be maintained in the older patient as the time between presentation of renal disease and malignancy is quite variable and can be of a lengthy duration (years).

The following discussion will concentrate on the treatment of the great majority of cases, i.e. the idiopathic membranous nephropathy category (IMGN). The natural history of untreated IMGN has been documented in several studies and must be known prior to considering therapy. Spontaneous remission occurs in 20–30% of IMGN cases, progressive renal failure in 20–40%, and the remaining patients retain mild to moderate proteinuria even after 5–10 years of observation. A summary of 11 studies demonstrated a 10-year survival rate of between 65% and 85%, and a recent pooled analysis of 32 reports indicated a 60% renal survival at 15 years. Understanding the natural history is further complicated by a spontaneous remitting and relapsing course in many patients. Complete remission can be seen in as many as 35% of the subjects of long-term (> 10 years) studies, with up to 50% having at least one relapse. A complete remission and a reduction in the relapse rate is more common in female patients and those with persistent subnephrotic-range proteinuria. In contrast, the male gender, age > 50 years, high levels of proteinuria (> 5 g/d), abnormal renal function at presentation and tubular interstitial disease on biopsy have all been associated with a poor prognosis.

PREDICTING OUTCOME

A method that accurately predicts outcome at an early stage of the disease would substantially aid in the management of the IMGN patient. A semi-quantitative method of predicting outcome has been developed and validated. It uses the clinical parameters of proteinuria and creatinine clearance estimates over fixed periods of time. In its simplest form, it demonstrated that the overall accuracy of predicting outcome when proteinuria values over 6-month time frames were persistently ≥ 4 g/d was 71%, ≥ 6 g/d was 79% and ≥ 8 g/d was 84%. If the
patient’s creatinine clearance was below normal at the beginning of these time periods and/or deterioration of renal function took place over the 6 months of observation, the accuracy was even higher. The advantages of the algorithm are its reliance on very few factors, all of which are standard measurements of renal function and its dynamic nature, i.e. the ability to repeatedly calculate the risk over the course of the patient’s disease. The issues of age, gender, degree of sclerosis on biopsy and hypertension are still important in the individual patient, but do not add to the predictive capacity of this model.

These observations on the natural history and our ability to predict outcome must be the background upon which current therapies are evaluated. This is particularly true given the substantial risk associated with most of our immune-modulating regimens. It therefore seems appropriate to segregate the patients studied to date into those that have a low risk and those that have a high risk of progression and then evaluate the published trials of different therapies based on their risk profile.

**RISK OF PROGRESSION CATEGORIES**

Low risk of progression patients have normal serum creatinine and creatinine clearance values and proteinuria < 3.5 g/d.

Medium-risk patients have normal or near normal creatinine and creatinine clearance values and persistent proteinuria over 6 months of between 3.5 and 6 g/d.

High-risk patients include those with moderate- to high-grade proteinuria (≥ 6 g/d) persistent over 6 months plus creatinine values either above normal or rising during the observation period. Additional features in this group may include hypertension and interstitial disease and/or glomerular obsolescence on renal biopsy.

**TREATMENT OPTIONS**

Treatment can be considered in four broad categories: (i) immunosuppressive therapy aimed at modulating the immune component of the disease, (ii) non-specific therapy focused on reducing proteinuria and, secondarily, slowing the progression to renal failure, (iii) treatment of the secondary effects of the disease on other systems, and (iv) treatment aimed at reducing the complications of immune-modulating drugs.

**Specific immunosuppression treatment**

**Low-risk patients**

The prognosis of patients with these criteria is excellent. In a series of over 300 cases from three distinct geographical regions followed for more than 5 years, only 5% went on to develop chronic renal insufficiency. Strategies to reduce protein excretion further and idealization of blood pressure through the use of agents such as angiotensin-converting enzyme inhibitors should be utilized. As the percentage that progresses is not zero, long-term follow-up should be maintained and include regular measurements of blood pressure, renal function and protein excretion. Immunosuppressive therapy is not recommended and, in the majority of cases, treatment of secondary effects of the disease is not required.

**Medium-risk patients**

Corticosteroids alone have been shown to be ineffective in inducing remissions of nephrotic syndrome in all controlled trials performed to date and in slowing progression in all but one trial. Although the follow-up periods were limited to less than 4 years and the dose and duration varied, the evidence indicates that these drugs alone should not be used in the management of this type of IMGN patient.

There is evidence of benefit when corticosteroids are combined with a cytotoxic agent. In a series of randomized trials from Italy, a significant increase in both partial and complete remissions in proteinuria and a reduction in the frequency of renal failure was observed.
Therapy consisted of 1 g of methylprednisolone i.v. on the first 3 d of months 1, 3 and 5, followed by 27 days of oral methylprednisolone at 0.4 mg/kg alternating in months 2, 4 and 6 with chlorambucil at 0.2 mg/kg/d. Utilizing this routine and following patients for up to 10 years, 40% of untreated patients reached end-stage renal disease compared with only 8% of the treated patients, and a non-nephrotic state was maintained during only 22% of the total follow-up time compared with 58% in the active drug group. When cyclophosphamide was substituted for the chlorambucil using the same study design a similar response was seen, although the follow-up was limited to 3 years. In this latter study, the relapse rate was substantial and occurred in approximately 30% of both groups within 2 years of treatment. This therapeutic regime proved to be quite safe, with only 10% of the patients stopping therapy owing to adverse affects.

**High-risk patients**

The percentage of IMGN patients in this category is small and very few have been the subject of randomized controlled trials. In a subgroup analysis of patients with initial renal insufficiency in one of the corticosteroid-alone trials, no difference was seen in the rate of deterioration over 4 years of follow-up. One small uncontrolled trial using pulse methylprednisolone for 5 d did show initial stabilization in 15 IMGN patients with renal failure, but, at follow-up, two had died and five had proceeded to end-stage renal disease, suggesting the benefit may be transient. Two small studies have used modifications of the Italian regimen in patients with IMGN with progressive renal insufficiency. One series showed approximately 50% of the 20 treated patients had an improvement, but the adverse event rate was high, even with an appropriate reduction in chlorambucil dosage. Cyclophosphamide combined with pulse methylprednisolone and oral prednisone has been compared with alternate-day prednisone alone in a randomized trial in such patients. There was no significant benefit observed by the addition of the cytotoxic agent.

In early uncontrolled studies, cyclosporine was associated with some benefit, but a high relapse rate, in this type of IMGN patient. A recent randomized controlled trial showed a significant reduction in proteinuria in the eight treated patients compared with the eight untreated patients that was sustained for up to 2 years in 50% of cases. The rate of progression was substantially slowed, as measured by an improvement in the slope of creatinine clearance of >60% during treatment. This drug is expensive and has nephrotoxic potential so monitoring for this and other adverse events must be part of any routine that includes this agent. Long-term oral cyclophosphamide with and without prednisone has been used in two smaller non-randomized trials. Both found benefit, but the risks of prolonged cytotoxic therapy, such as infertility, infection and malignancy, are significant and have limited this approach.

**Non-immunological treatment**

Dietary protein restriction has not been shown to be associated with a complete remission of the nephrotic syndrome. However, most dietary protein restriction trials have shown that maximum benefit accrues in those patients with the heaviest proteinuria. Certainly many IMGN patients would fulfil this criterion.

Blood pressure reduction does improve proteinuria, and angiotensin-converting enzyme inhibitors have been shown to reduce urine protein excretion in excess of their anti-hypertensive effect in several studies of patients with diabetic and non-diabetic glomerular diseases. An additional benefit has also been demonstrated in IMGN patients, but the studies have been small, uncontrolled and with limited follow-up. The mechanism for the anti-proteinuric effect is not fully understood, but it does not appear to involve merely a reduction in glomerular filtration rate.

**Treatment of the secondary effects of the disease**

Attention must be paid to the associated hyperlipidaemia and increased risk of thromboembolism in patients with persistent heavy proteinuria and/or impaired renal function. The group with the nephrotic syndrome will have elevated serum cholesterol and triglyceride values and normal or low levels of high-density lipoproteins (HDL) and increased low-density (LDL). This probably plays a central role in the increased risk of cardiovascular disease in such patients. Although no randomized trial has been carried out in this specific group, HMG Co-A reductase inhibitors have been shown to be safe and effective and many clinicians apply evidence from the non-renal disease literature to advocate their use in these patients.

Studies of the risk of thrombotic disease in IMGN have shown a wide variation in prevalence, partly related to the rigour of screening and partly to the detection methods used. In a recent review, deep venous thromboses were reported in 11%, clinically significant pulmonary emboli in 11% and renal vein thrombosis in 35% of IMGN patients. Other studies have reported a lower rate and a higher than average risk associated with long-term anticoagulant therapy, perhaps related to the commonly associated hypoalbuminaemia state. No consensus has emerged whether prophylactic anticoagulation should be used, although if the former figures are correct and the results are viewed in the light of data from patients receiving anticoagulants in other populations, the benefits would appear to outweigh the risks. The
majority of nephrologists today use this therapy as primary prevention only in high-risk cases and reserve its general use until after documentation of a thromboembolic event.

Treatment prophylaxis

Several large studies in the renal transplant field and in post-menopausal women have indicated that agents such as biphosphonates reduce bone loss during long-term use of corticosteroids. Utilization of such therapy in the IMGN patient should be considered when the course of therapy includes prolonged prednisone treatment. Trimethoprim-sulphamethoxazole has reduced the incidence of Pneumocystis carinii pneumonia (PCP) in patients on prolonged immunosuppressive therapy in both the transplant field and in certain autoimmune diseases. Its use when IMGN patients are exposed to prolonged cytotoxic agents seems prudent.

MANAGEMENT PLAN

Figure 1 gives a graphic display of a treatment algorithm for patients with IMGN. In addition, the following general rules should be applied:
1) Establish whether the disease is primary or secondary and take appropriate actions for known causes.
2) In the majority of cases, the patient’s renal function should be monitored over a 6-month period utilizing maximum conservative (non-immunosuppressive) therapy and a risk of progression score established.
3) If persistent high-grade proteinuria and/or deterioration in renal function continues, despite maximum conservative therapy, introduce treatment for the secondary effects of the disease, such as a lipid-lowering agent and possibly anticoagulants.
4) The first choice of specific therapy for medium risk of progression patients is the chlorambucil or cyclophosphamide/prednisone routine for 6 months.
5) Specific therapy for high-risk patients should be either the modified chlorambucil/prednisone routine or cyclosporin for 6–12 months.
6) Introduce risk reduction strategies, such as biphosphonates or other agents, when long-term corticosteroids are used, and trimethoprim-sulphamethoxazole if long-term immunosuppressive drugs are employed.
7) If both specific therapies fail and the clinical status warrants further attempts at treatment, consider cyclophosphamide alone for a maximum of 6–12 months.

REFERENCES
2. Honkanen E, Tornroth T, Gronhagen-Riska C. Natural history,